



THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Cantor *et al.*

Serial No.: 09/395,409

Confirmation No.: 6005

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For: SOLID PHASE SEQUENCING OF  
BIOPOLYMERS

Art Unit: 1655

Examiner: Chakrabarti, A.

AMENDMENT

Commissioner for Patents  
P. O. Box 2327  
Arlington, VA 22202

Dear Sir:

Responsive to the Office Action, mailed January 22, 2002, consideration of the following remarks and entry of the following amendments are respectfully requested.

IN THE CLAIMS:

Please cancel claims 77 and 126 without prejudice or disclaimer.

Please replace claims 67, 71 and 125 with amended claims 67, 61 and 125 as follows:

67. (Twice Amended) The method of claim 64, wherein each probe is attached to the solid support by a bond selected from the group consisting of a covalent bond, an electrostatic bond, a hydrogen bond, a cleavable bond, a photocleavable bond, a disulfide bond, a peptide bond, a diester bond, a selectively releasable bond and combinations thereof.

71. (Twice Amended) The method of claim 67, wherein the bond is a selectively releasable bond and comprises 4, 4'-dimethoxytrityl or a derivative thereof.

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125. (Twice Amended) The array of claim 124, wherein:  
the array comprises a nucleic acid probe having at least one mass-modifying functionality.

**REMARKS**

A check for fee for a three-month extension is attached hereto. Any fees that are due with this paper or application can be charged to Deposit Account No. 50-1213. If a Petition for extension of time is due, this paper can be considered such Petition.

Claims 1-55, 58-60, 63-76, 86, 88-125, 127 and 128 are presently pending in this application. Claims 77 and 126 are cancelled herein without prejudice or disclaimer. Applicant reserves the right to prosecute any subject matter thereof in a continuing application. Claims 67 and 71 are amended to correct minor grammatical errors in order to more distinctly describe the claimed subject matter. Claim 125 is amended to depend from claim 124. A marked up copy per 37 C.F.R. §1.121 showing changes made to the claim is attached to this response. No amendments are made to change to scope or content of the claim nor to avoid any art of record.

**THE REJECTION OF CLAIMS 71 and 72 UNDER 35 U.S.C. §112, SECOND PARAGRAPH**

Claims 71 and 72 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the claimed subject matter because the Examiner contends (1) that there is insufficient antecedent basis for the limitation "the selectively releasable" in claim 71, and (2) that the recitation "releasable" in claim 71 allegedly "renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention." The rejection is respectfully traversed.

**RELEVANT LAW**

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings

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of prior art, and (3) the interpretation claims would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Claims need only "reasonably apprise those skilled in the art" of their scope and be "as precise as the subject permits." Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986), cert. den., 480 U.S. 947 (1987). The Court in Orthokinetics, Inc v. Safety Travel Chairs, Inc., 1 USPQ2d 1081 (Fed. Cir. 1986) held that a claim limitation requiring that a pediatric wheelchair part be "so dimensioned as to be insertable through the space between the doorframe of an automobile and one of the seats" is definite. The Court stated:

The phrase "so dimensioned" is as accurate as the subject matter permits, automobiles being of various sizes. As long as those of ordinary skill in the art realized that the dimensions could be easily obtained, § 112, 2d ¶ requires nothing more. The patent law does not require that all possible lengths corresponding to the spaces in hundreds of different automobiles be listed in the patent, let alone that they be listed in the claims.

1 USPQ2d at 1088.

When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

35 U.S.C. §112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. The claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. Shatterproof Glass Corp.v. Libby-Owens Ford Col, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir), cert dismissed, 106 S. Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular subject matter and the prior art. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

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[i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (Bendix Corp. v United States, 600 F.2d 1364, 1369, 220 Ct. Cl. 507,514, 204 USPQ 617, 621 (1979); See, also, Carl Zeiss Stiftung v. Renishaw plc, 20 USPQ2d 1094, 1101).

## **THE CLAIMS**

Claim 71 depends from claim 67, which recites a Markush group in which one of the alternatives is a "selectively releasable bond." Claim 71 depends upon claim 67 and recites that the bond is a selectively releasable bond and it comprises 4,4'-dimethoxytrityl or a derivative thereof.

## **ANALYSIS**

It is respectfully submitted that claim 67, from which claim 71 depends, includes the recitation "selectively releasable bond," and therefore claim 67 provides the requisite antecedent basis for this recitation in claim 71.

The Examiner's contention that the recitation "releasable" renders the claim indefinite "because it is unclear whether the limitation(s) following the phrase are part of the claimed invention" is without merit. Claim 71 as amended depends from claim 67, which is directed to an embodiment of the method of claim 64 where each probe is attached to the solid support by a bond selected from the group consisting of a covalent bond, an electrostatic bond, a hydrogen bond, a cleavable bond, a photocleavable bond, a disulfide bond, a peptide bond, a diester bond, a selectively releasable bond and combinations thereof. One of skill in the art would understand it serves as the antecedent for the recitation of selectively releasable bond in claim 71, and that such bond includes 4,4'-dimethoxytrityl or a derivative thereof.

## **THE REJECTION OF CLAIMS 1-27, 29-55, 58-60, 63-70, 73-77, 86, and 88-128 UNDER 35 U.S.C. §102(e)**

Claims 1-27, 29-55, 58-60, 63-70, 73-77, 86, and 88-128 are rejected under 35 U.S.C. § 102(e) as anticipated by Köster *et al.* (U.S. Patent 5,605,798) because Köster *et al.* allegedly discloses a method for sequencing a target nucleic acid that includes (a) providing a set of nucleic acid fragments

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each containing a sequence that corresponds to a sequence of the target nucleic acid; (b) hybridizing the set to an array of nucleic acid probes to form an array of nucleic acids, where each probe includes a single-stranded portion including a variable region; and (c) determining the molecular weights for the nucleic acids of the target array by mass spectrometry, whereby the sequence of the target nucleic acid is determined. It is further alleged that Köster *et al.* discloses use of electrophoresis for molecular weight determination, mass spectrometry by MALDI and TOF, and simultaneous determination of the molecular weight of two or more samples.

This rejection is respectfully traversed. It is respectfully submitted that the grounds for this rejection are moot with respect to claims 77 and 126, which are cancelled herein without prejudice or disclaimer.

**RELEVANT LAW**

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundsciber Corp. v. U.S. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

## THE CLAIMS

Independent claim 1 and its dependent claims (2-55, 58-60, 63-76, 88-123) are directed to methods of **sequencing** a target nucleic acid molecule by hybridizing an array of probes, which each contain a variable region, to fragments of the target nucleic acid, determining the molecular weight of the members of the resulting hybridized array and thereby determining the sequence of the target nucleic acid. Dependent claims specify the manner in which the molecular weight is determined.

Claims 124 and 125 are directed to arrays of probes that include a single-stranded portion which has a variable region of length R and a double-stranded portion, where the array is attached to a solid support that includes matrix for mass spectrometry. Claim 124 recites that there are  $4^R$  probes, where R is the length of the variable region. Claim 125 specifies that a probe includes a mass-modifying functionality. Dependent claim 127 and its dependent claim are directed to a system which includes a mass spectrometer, a computer, and the array of claim 124.

### Disclosure of Köster *et al.* (5,605,798)

Köster discloses processes for detecting a target nucleic acid in a sample, by detecting a nucleic acid molecule by its molecular weight by mass spectrometry. Köster does not disclose a process or method for sequencing. The method of detection does not involve hybridizing fragments of a target nucleic acid molecule to an array of probes each of which includes a single-stranded portion a variable sequence, and it does not involve determination of the molecular weight of hybridized members of any array and then deducing the **sequence** of the target. For detection, mass spectrometry is used to detect the presence of a nucleic acid molecule. In contrast, sequencing involves the identification of a number of nucleic acid molecules from which the sequence is deduced. In particular, in the claimed method, the target is hybridized to a plurality of probes, which hybridize to it by virtue of complementary nucleic acid

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present in a plurality of probes. In the claimed methods, is from the **pattern** of hybridization that the sequence can be determined; in contrast in detection methods, it is from the **fact** of hybridization that detection is effected. Hence detection and sequencing are distinct and very different processes.

Further, Köster does not disclose a collection of 4<sup>R</sup> probes where each probe includes a single-stranded portion that has a variable region of length R, where R is the length of the variable region of the single-stranded portion of the probe.

**ANALYSIS**

**Claim 1 and its dependents**

As noted, while independent claim 1 and its dependent claims (2-55, 58-60, 63-76, 88-123, and 128) are directed to methods, they are not directed to methods of "detection" as stated in the Office Action, but instead are directed to methods of **sequencing** a target nucleic acid. Each claim specifies that the sequence of the target is determined by virtue of determination of molecular weights of members of the hybridized array.

Köster, U.S. Patent 5,605,798, states that the claimed subject matter "provides mass spectrometric processes for **detecting** a particular nucleic acid sequence in a biological sample" (col. 7, lines 19-21, emphasis added). Köster '798 does not deduce the sequence of the nucleic acid, and thus it does not disclose a method of sequencing a target nucleic acid. As discussed above, in the claimed methods, is from the **pattern** of hybridization (*i.e.*, the probes that hybridize to the target) that the sequence can be determined; in contrast in detection methods, it is from the **fact** of hybridization of the target to a particular probe.

Because Köster '798 does not disclose sequencing a target nucleic acid, '798 does not anticipate any of claims 1-27, 29-55, 58-60, 63-70, 73-76.

**Claims 124 and 125**

Claims 124 and claims dependent thereon are directed to arrays of  $4^R$  probes that include a single-stranded portion, which has a variable region of length  $R$ , where the array is attached to a solid support that includes matrix for mass spectrometry. Köster '798 does not disclose an array of  $4^R$  probes, each of which includes a single-stranded portion that contains a variable sequence of length  $R$ . Therefore Köster does not anticipate any of claims 86, 88, 89 and 124-127.

**REBUTTAL TO EXAMINER'S ARGUMENTS**

**1) Sequencing**

The Examiner alleges that Köster discloses a method for sequencing a target nucleic acid by providing a set of nucleic acid fragments each containing a sequence corresponding to a sequence of the target nucleic acid, hybridizing this set of nucleic acid fragments to an array of nucleic acid probes where each probe comprises a single-stranded portion comprising a variable region, which forms a target array of nucleic acids, and determining the molecular weights for the nucleic acids of the target array by mass spectrometry. Applicant respectfully disagrees.

As discussed above, Köster discloses processes for detecting a target nucleic acid in a sample, not a process or method for sequencing a target nucleic acid. The methods as claimed in this application require hybridizing it to an array of probes that include a variable portion, which includes  $4^R$  probes constituting all possible permutations of a sequence of a sequence of length  $R$ , determining the molecular weights of the members of the hybridized array to determine to which the target hybridizes and thereby deducing the sequence of the target, based upon the probes to which the target hybridizes.

As noted, Köster is directed to methods of **detection** of target nucleic acids using mass spectrometry. A variety of specific exemplary embodiments are described. The methods, however, do not involve sequencing of the target

nor do they involve hybridizing to arrays of probes that contain variable regions, particularly variable regions of length R. In its basic embodiment, it is directed to a method for detecting the presence of a nucleic acid molecule target in a sample, by detecting its presence based upon its molecular weight. This process does not involved hybridization to a plurality of probes nor deduction of a sequence based upon the hybridization pattern.

Köster contains no reference to methods of sequencing, but to methods of detecting a target nucleic acid (see, for example, col. 3, lines 51-53 and 60; col. 5, lines 19-21 and 43-45; col. 7, lines 19-21; col. 10, lines 47-52; col. 11, lines 46 and 49-51 and 57-59). For example, the '798 specification states that "the process of this invention makes use of known sequence information of the target sequence and known mutation sites" (col. 12, lines 14-16) and that "[d]etection of hybridization and the molecular weights of the captured target sequences provide information on whether and where in a gene a mutation is present" (col. 12, lines 24-26). Claim 1 of 5,605,798 states that the claimed subject matter is "[a] process for detecting a target nucleic acid sequence" and not a method of sequencing as the Examiner alleges.

**2) Array of Probes With Single-Stranded Portion Containing a Variable Sequence and a Constant Sequence**

The Examiner alleges that Köster discloses an array of nucleic acid probes where each probe comprises a single-stranded portion comprising a variable region, citing as support for the allegation "Example 1 and claim 1 and Figure 1 and Column 4, lines 11-14 and Column 9, lines 28-43, and Figures 2-3."

Example 1 describes hybridization of an oligonucleotide to immobilized oligonucleotides and shows that a hybridized oligonucleotide can be detected by mass spectrometry. Example 1 is directed to an embodiment where a 50

nucleotide sequence (50mer) attached to controlled pore glass beads serves as a template for separate hybridizations with a 26mer or a 46mer (col. 12, line 53).

Oligo-nucleotide not bound to the polymer-bound template is removed by

centrifugation and washing, and the beads are mixed with matrix and analyzed by MALDI-TOF mass spectrometry.

If, *arguendo*, the 50mer attached to the glass beads is construed as a probe as used in the instant application, there is no variable region — the same 50mer is attached to each of the controlled pore glass beads, and hence the sequence is identical. Even if, conversely, the 26mer or the 46mer were considered the probe, again there is no variable region, as the sequence of both the 26mer and the 46mer remains unvaried. Furthermore, Example 1 was provided to show that it is possible to capture a detector nucleic acid molecule on a solid support which is presenting a target molecule, and then detecting the hybridized detector by mass spectrometry.

Claim 1 recites:

1. A process for detecting a target nucleic acid sequence present in a biological sample, comprising the steps of:
  - a) obtaining a nucleic acid molecule containing a target nucleic acid sequence from a biological sample;
  - b) hybridizing a detector oligonucleotide with the target nucleic acid sequence, wherein at least one of the detector oligonucleotide or the target nucleic acid sequence has been conditioned;
  - c) removing unhybridized detector oligonucleotide;
  - d) ionizing and volatilizing the product of step c); and
  - e) detecting the detector oligonucleotide by mass spectrometry, wherein detection of the detector oligonucleotide indicates the presence of the target nucleic acid sequence in the biological sample.

Claim 1 is directed to an embodiment of a process for detecting a target nucleic acid that includes the steps of obtaining nucleic acid molecule containing a target nucleic acid sequence and hybridizing a detector oligonucleotide to the target, and then detecting the detector, where detection of the detector indicates that the target is present in the sample. Even if we assume *arguendo* that the detector oligonucleotide of Köster '798 is equivalent to the instantly claimed "probe," claim 1 of '798 makes no mention of arrays with 4<sup>R</sup> probes as

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in instant claim 124 and dependents. Claim 2 specifies that the **target** nucleic acid **not the probe** is immobilized.

Figure 1 of '798 shows a process for performing MS analysis on a target detection site (TDS) contained within a target nucleic acid molecule (T). A specific capture sequence (C) (Figs. 1A and 1C) or the target containing a detection site (Fig. 1B) is attached to a solid support (SS) via a spacer (S). The capture sequence (C) hybridizes with a complementary sequence on the target nucleic acid molecule. Hybridization between the detector nucleic acid sequence and the detector site can be detected by MS. None of Figure 1A through 1C shows an array of probes, but instead show only a single oligonucleotide attached to a solid support. None of Figs. 1A-C show a probe containing a single-stranded portion containing a variable region.

Embodiments in which there are a plurality of target molecules or other molecules immobilized are for multiplexing, which involves detection of a plurality of different target nucleic acid molecules in a sample.

Köster '798 discloses that a plurality of targets can be arranged in a format that allows multiple simultaneous detections (col. 4, lines 11-14), and the Examiner alleges that this "multiplexing" (as further described in col. 9, lines 28-43, and illustrated in Figs. 2-3) discloses an array of probes each of which contains a single-stranded portion containing a variable region.

This method does not meet the limitations of any of the present method claims, which require deduction of the sequence of a target. It does not meet the limitations of the array claims, which require  $4^R$  probes of length R.

Furthermore, the specification at col. 9, lines 28-43 of Köster does not disclose an array of probes each of which contains a single-stranded portion containing a constant region and a variable region, and clearly does not disclose teach or suggest an array in which there is a variable region of length R. For example, Figure 3 illustrates an array of probes, each containing a different

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capture sequence, C1 through C<sub>n</sub>, to accomplish differentiation (col. 5, lines 52-62).

**3) Array of Probes Each of Which Includes a Single- and Double-Stranded Region**

The Examiner alleges that Köster discloses Figure 3, an array of nucleic acid probes where each probe comprises a single-stranded portion and a double-stranded portion. As discussed above, Köster does not disclose the instantly claimed methods of sequencing, nor an array that contains 4<sup>R</sup> probes with a variable region of length R. With respect to Figure 3, Köster states:

Fig. 3 is a diagram showing still another multiplex detection format. In this embodiment, differentiation is accomplished by employing different specific capture sequences which are position-specifically immobilized on a flat surface (e.g., a "chip array"). If different target sequences T1-T<sub>n</sub> are present, their target capture sites TCS1-TCS<sub>n</sub> will interact with complementary immobilized capture sequences C1-C<sub>n</sub>. Detection is achieved by employing appropriately mass differentiated detector oligonucleotides D1-D<sub>n</sub>, which are mass differentiated either by their sequences or by mass modifying functionalities M1-M<sub>n</sub>.

Köster discloses an array of probes attached to a solid support through a spacer moiety, where each probe contains a different capture moiety. As disclosed in the specification, the probe disclosed by Köster does not contain a single-stranded region variable region of length R, and a double-stranded region. Each probe instead includes a spacer moiety and a capture sequence, and there is no mention of a double-stranded portion of the probe, nor is there a "variable" region nor are there 4<sup>R</sup> probes. Furthermore, Köster does not disclose teach or suggest that hybridization of "a set of nucleic acid fragments each containing a sequence that corresponds to a sequence of the target nucleic acid" to an array of any sort of probes. The embodiments in which arrays of probes are used, are those in which multiplexing, *i.e.*, detection of a plurality of different targets simultaneously, is contemplated.

It appears that the Examiner is alleging that the "probes" of Köster's array are to be construed as including the spacer moiety, the capture sequence, and

the subsequently captured nucleic acid sequence, allegedly thereby yielding a probe that contains a double-stranded region (the capture region  $C_n$  bound to the complementary target capture sequence  $TCS_n$ ) and a single-stranded region (the target detector sequence,  $TDS_n$ ). As noted, even if this were a correct analogy, which it is not, Köster does not disclose an array of  $4^R$  probes, each having a variable region of length R.

Further, even using the logic of the Examiner, however, applicants argue that the target detector sequence is subsequently hybridized to a detector oligonucleotide  $D_n$ , and consequently become double-stranded, thereby resulting in a probe that contains no single-stranded regions. If the detector oligonucleotide hybrids to the target detector site or the target prior to or contemporaneous with the hybridization of the target to the probe, there would be no single-stranded region. Further, once the target nucleic acid is attached to the probe, the "probe" no longer can no longer function as a probe, because its capture site is occupied. Only after release of the target nucleic acid with the material attached to the solid support be able to capture a target nucleic acid. Once the target nucleic acid is released from the probe disclosed by Köster, however, there is no double-stranded region.

**4) Array of Probes with  $4^R$  Probes**

The Examiner alleges that Köster discloses, in Figures 1-3, an array of nucleic acid probes containing  $4^R$  probes, where each probe includes a single-stranded portion and a double-stranded portion, where R is the length of the variable region. Köster does not disclose the length of a "variable region" — the recitation "variable" or "variable region" does not appear in the specification of Köster '798. The disclosure discusses the requirement that the molecular weight difference between detector nucleotides for multiplexing must be large enough so that simultaneous detection can be achieved and Köster discloses that this can be achieved the sequence itself, by composition or length (col. 5, lines 43-51).

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Köster discloses that a spacer region of at least five nucleotides in length between the solid support and the capture nucleic acid sequence is required to allow complementation without hinderance by the support (col. 8, lines 3-8). No other discussion of length is contained in the disclosure. Hence, Köster does not disclose the length of the variable region of the probe, or an array of probes containing  $4^R$  probes, where R is the length of the variable region.

**5 An Array of Probes With Sufficient Sequence Diversity in the Variable Regions to Hybridize All of the Target Sequence With Complete Discrimination**

The Examiner alleges that Köster discloses an array of nucleic acid probes with sufficient sequence diversity in the variable regions to hybridize all of the target sequence with complete discrimination, citing as support for the allegation "Example 1 and claim 1 and Figure 1 and Column 4, lines 11-14 and Column 9, lines 28-43, and Figures 2-3.". Applicant respectfully disagrees. As discussed above, the recitations "variable" or "variable region" do not appear in the specification of Köster '798. Similarly, the recitations "diversity" or "sequence diversity" do not appear in the specification of Köster '798. Claim 1 of Köster does not discuss an array of probes with sufficient sequence diversity to hybridize all of the target sequence. None of Figures 1A-C, 2, or 3 support the Examiner's allegation. Figure 1 does not show an array of probes.

Köster discloses multiplexing for **detecting** the presence of a plurality of **different** target nucleic acid molecules in a sample simultaneously. This is **not** sequencing. In embodiments in Köster where target detection sequences are arranged in a format that allows multiple simultaneous detections (col. 4, lines 11-14 and col. 9, lines 28-43), different target molecules are captured or immobilized on a support; there is no disclosure of an array with a plurality of **probes with variable regions that include all possible sequences that correspond to a target nucleic acid molecule.**

Köster discloses that multiplexing allows simultaneous detection of, for example, more than one (mutated) loci on a particular captured nucleic acid

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fragment or parallel processing using multiple arrays (col. 9, lines 28-43) for detection. The reference does not disclose that multiplexing involves an array of probes with sufficient sequence diversity to hybridize to all of the target sequence; nor would such make any sense in the context of detection (diagnostics) that does not involve sequencing. Figure 2 does not disclose an array of probes. As discussed previously, Figure 3 shows an array of probes of various capture regions,  $C_n$ . Köster discloses that **detection of different target sequences**  $T1-T_n$  can be accomplished by complementary immobilization of such target nucleic acids on probes containing the corresponding capture sequences  $C1-C_n$ , using appropriately mass differentiated detector oligonucleotides  $D1-D_n$  (col. 5, lines 52-62). Hence, Köster discloses that a large number of different target nucleic acids can be detected simultaneously using appropriate selection of capture sequences and detector oligonucleotides. Köster does not disclose using an array of probes with sufficient diversity in the variable region of each probe so as to hybridize with the complete sequence of a target (it is the target that is immobilized in Köster) thereby allowing the determination of the sequence of the target nucleic acid.

**THE REJECTION OF CLAIMS 1-55, 58-60, 63-70, 73-77, 86, AND 88-128 UNDER 35 U.S.C. §103(a)**

Claims 1-55, 58-60, 63-70, 73-77, 86 and 88-128 are rejected under 35 U.S.C. §103(a) as being unpatentable over Köster (U.S. Patent 5,605,798) in view of Weiss (U.S. Patent 6,025,193) because Köster allegedly teaches claims 1-27, 29-55, 58-60, 63-70, 73-77, 86, and 88-128, but does not teach the generation of a thiol moiety by using Beucage reagent as claimed in claim 28. Weiss is alleged to cure this defect. The rejection is respectfully traversed.

**RELEVANT LAW**

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329,

933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

#### THE CLAIMS

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See related section above (page 7). Claim 28 depends from 27, which depends ultimately from claim 1, and is directed to an embodiment of a method of sequencing of claim 1 wherein the array includes nucleic acid probes having a thiol mass-modifying moiety generated by using Beucage reagent.

**Differences between the cited references and the claimed subject matter**

**Köster (U.S. Patent 5,605,798)**

See related section above (pages 7-8).

**Weiss (U.S. Patent 6,025,193)**

Weiss teaches methods and compositions for diagnosing and treating pathological conditions related to a dopamine receptor abnormality, which includes administering a plasmid encoding an oligonucleotide anti-sense to one or more RNA molecules encoding one of the several dopamine receptors. The reference teaches that unmodified oligodeoxynucleotides can be converted into phosphorothioate oligodeoxynucleotides using standard phosphoramidite protocols but replacing the standard oxidation by iodine with Beucage reagent for sulfurization. Weiss teaches that using Beucage reagent results in the replacement of every oxygen group of the phosphodiester bond with a sulfur group, and that such substitutions result in an asymmetric distribution of the negative charge to predominate on the sulfur atom, resulting in "improved stability to nucleases, retention of solubility in water and stability to base-catalyzed hydrolysis" (col. 13, lines 2-14), improved biodistribution and *in vivo* stability (col. 15, lines 41-45), and activation of Rnase H, and thus are potentially useful therapeutic agents (col. 13, lines 45-47).

Weiss does not teach or suggest the use of mass spectrometry for sequencing nucleic acids. Weiss does not teach an array of nucleic acid probes each of which includes a single-stranded portion and a double-stranded portion. The reference does not teach or suggest a method for detecting or determining the sequence of the target nucleic acid by determining the molecular weights for nucleic acids of such an array.

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**ANALYSIS**

**The Office Action fails to establish that the claims are *prima facie* obvious for the following reasons.**

**The combination of cited references does not result in the instantly claimed methods**

Claims 1-27, 29-55, 58-60, 63-70, 73-76 of the instant application are directed to a method for sequencing a target nucleic acid. As discussed above (see page 8), Köster '798 does not teach or suggest a method for sequencing a target nucleic acid, and Weiss does not cure this defect. Weiss does not teach or suggest a method of sequencing a target nucleic acid. Thus, neither Köster nor Weiss, singly or in combination, teaches sequencing a target nucleic acid, and therefore the combination of Köster and Weiss fails to teach all the elements of the subject matter of claims 1-27, 29-55, 58-60, 63-70, 73-76 of the instant application.

Claims 124 and its dependents are directed to arrays of 4<sup>R</sup> probes that include a single-stranded portion, which has a variable region of length R, and a double-stranded portion, where the array is attached to a solid support and includes matrix for mass spectrometry. As discussed above, Köster '798 does not teach or suggest an array of 4<sup>R</sup> probes each of which includes a single-stranded portion and a double-stranded portion, and Weiss does not cure this defect. Thus, the combination of Köster and Weiss fails to teach all the elements of the subject matter of instant claims 124 and claims dependent thereon.

Claim 127 and its dependent claims (86, 88, and 89) are directed to a system that includes a mass spectrometer, a computer, and the array of claim 124. As discussed above, Köster does not teach or suggest an array as claimed in claim 124, and Weiss does not cure this defect. Thus, the combination of

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Köster and Weiss fails to teach all the elements of the subject matter of instant claims 86, 88-89, and 127.

Therefore, the Examiner has failed to set forth a prima facie case of obviousness and the rejection should be withdrawn.

**THE REJECTION OF CLAIMS 1-55, 58-60, 63-70, 73-77, 86, AND 88-128 UNDER 35 U.S.C. §103(a)**

Claims 1-55, 58-60, 63-70, 73-77, 86 and 88-128 are rejected under 35 U.S.C. §103(a) as being unpatentable over Köster (U.S. Patent 5,605,798) in view of Sanghvi *et al.* (U.S. Patent 6,214,551) because the Examiner contends that Köster teaches every element of claims 1-27, 29-55, 58-60, 63-70, 73-77, 86, and 88-128 as alleged above, and although Köster does not teach the selectively releasable bonds claimed in claims 71 and 72, it is alleged that Sanghvi *et al.* cures this defect.

The rejection is respectfully traversed.

**RELEVANT LAW**

See related section above (pages 10-11).

**THE CLAIMS**

See related sections above (pages 3 and 7).

**Differences between the cited references and the claimed subject matter**

**Köster (U.S. Patent 5,605,798)**

See related section above (pages 7-8).

**Sanghvi *et al.* (U.S. Patent 6,214,551)**

Sanghvi *et al.* teaches compounds that mimic and/or modulate the activity of wild-type nucleic acids. The compounds taught by Sanghvi *et al.* contain a selected nucleoside sequence where the nucleosides are covalently bound through linking groups that contain adjacent nitrogen atoms. Sanghvi *et al.* teaches the use of dimethoxytrityl groups as a blocking group during nucleoside polymerization.

The reference does not teach or suggest the use of dimethoxytrityl or a derivative thereof as a selectively releasable bond by which to attach a probe to a solid support, as claimed in the instant application. Instead, Sanghvi *et al.* teaches that an oligonucleotide is tethered to a solid support via its 3' hydroxyl group (col. 57, line 63 through col. 58, line 14).

Sanghvi *et al.* does not teach or suggest the use of mass spectrometry, or using mass spectrometry for sequencing nucleic acids, or hybridizing a set of nucleic acid fragments containing a sequence that corresponds to a sequence of the target nucleic acid to an array of nucleic acid probes to form a target array of nucleic acids, nor does it teach or suggest an array of probes each of which includes a single-stranded portion and a double-stranded portion. Sanghvi *et al.* does not teach or suggest determining the molecular weights for nucleic acids of the target array, or a method for determining the sequence of the target nucleic acid.

## ANALYSIS

### **The combination of cited references does not result in the instantly claimed methods**

The combination of the teachings of Köster with Sanghvi *et al.* does not result in the subject matter of the pending claims. As discussed above (see page 8), Köster does not teach a method of sequencing a target nucleic acid, and Sanghvi *et al.* does not cure this defect because Sanghvi *et al.* does not teach or suggest a method for sequencing a target nucleic acid. Thus, neither Köster nor Sanghvi *et al.*, singly or in combination, teaches sequencing a target nucleic acid, and therefore the combination of Köster and Sanghvi *et al.* fails to teach all the elements of the subject matter of claims 1-27, 29-55, 58-60, 63-70, 73-76 of the instant application.

Furthermore, with respect to claims 124 and its dependents, as discussed above, Köster does not teach or suggest an array of 4<sup>R</sup> probes each of which includes a single-stranded portion and a double-stranded portion and Sanghvi *et*

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*al.* does not cure these defects. Sanghvi *et al.* does not teach or suggest such an array of probes where each probe includes a single-stranded portion and a double-stranded portion. Thus, the combination of Köster and Sanghvi *et al.* fails to teach all the elements of the subject matter of instant claims 124 claims dependent thereon.

Köster does not teach or suggest a system that includes a mass spectrometer, a computer, and the array of claim 124 and Sanghvi *et al.* does not cure this defect. Thus, neither Köster nor Sanghvi *et al.*, singly or in combination, teaches the claimed system, and therefore the combination of Köster and Weiss fails to teach all the elements of the subject matter of instant claims 86, 88-89, and 127.

Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

**Joint Inventors (102(f) and 102(g))**

The instant application, which is a continuation of U.S. patent application Serial Nos. 08/420,009, 08/470,835, 08/419,994, and 08/470,716, designates as joint inventors: Charles R. Cantor and Hubert Köster, each of whom was subject to an obligation to assign to a different entity. Applicant is aware of the obligation imposed by 37 C.F.R. §1.56 and is currently investigating the inventorship of each of the claims. If the Office, however, believes that a rejection of any claims based upon 35 U.S.C. §102(f) and/or 102(g) can be made if claims have different inventors, the Office is invited to do so. At this time, it is believed that, even if all claims do not have the same date of invention and are not the joint invention of Drs. Cantor and Köster, but the sole invention of either, no sustainable rejection of any claims can be set forth.

\* \* \*

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**AMENDMENT**

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,  
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